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     (FILE 'HOME' ENTERED AT 12:30:06 ON 26 APR 2007)

     FILE 'CAPLUS, EMBASE' ENTERED AT 12:31:32 ON 26 APR 2007
L1          1164 S SAPONIN? AND ADJUVANT
L2           213 S L1 AND PY<1993
L3           175 DUPLICATE REMOVE L2 (38 DUPLICATES REMOVED)
L4            41 S L3 AND (CLOSTRIDIA OR VIRUS OR VIRAL)

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WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Thursday, April 26, 2007

Hide?	Set Name	Query	Hit Count
		DB=DWPI,JPAB,EPAB,USOC,USPT,PGPB; PLUR=YES; OP=OR	
☐	L1	(QUILA | QUILAIASAPONIN | QUILAJASAPONIN | QUILAIA)!	303
☐	L2	(QUIL-A | QUIL-A-CONTAINING | "QUIL-A.RTM")!	173
☐	L3	(SAPONIN | SAPONINBEARING | SAPONINC | SAPONINAS | SAPONINABLE | SAPONINAND | SAPONINANIO | SAPONINAV)!	13806
☐	L4	(SAPONINCOMPOUND | SAPONINCONTAININ | SAPONINCONTAINING | SAPONINE)!	597
☐	L5	(SAPONINCOMPOUND | SAPONINCONTAININ | SAPONINCONTAINING | SAPONINE)!	597
☐	L6	(SAPONINEDETOXICATING | SAPONINEMULSION | SAPONINES | SAPONINE-CONTAINING)!	167
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; PLUR=YES; OP=OR	
☐	L7	L1 L2 L3 L4 L5 L6	14637
☐	L8	L7 and ay>1994	14637
☐	L9	L7 and @ay>1994	8264
☐	L10	L8 not l9	6373
☐	L11	L7.ti,ab,clm.	4128
☐	L12	L11 and l10	1757
☐	L13	l11 and @ay>1994	2371
☐	L14	L11 not L13	1757
☐	L15	L14 and (clostrid$ or virus or viral or pathogen or pathogenic or microbe or microbial or microorganism or organism)	174
☐	L16	l15 and @ay>1993	27
☐	L17	l15 not L16	147
☐	L18	l17 and (tetani or tetanus! or clostrid$)	7

END OF SEARCH HISTORY

☐ 3. Document ID: US 5403586 A

L18: Entry 3 of 7 File: USPT Apr 4, 1995

DOCUMENT-IDENTIFIER: US 5403586 A
TITLE: LHRH-TraTp fusion proteins

Brief Summary Text (52):
Preferred polynucleotide molecules are recombinant DNA molecules. More preferably, the recombinant DNA molecules comprise plasmid vectors. A preferred vector is pBTA 812. It will be recognised that vectors other than plasmid vectors could be used. Other vectors include other expression systems including viral, cosmid and phasmid vectors.

Detailed Description Text (75):
Notwithstanding the specific uses exemplified in this specification, the approach used here with regard to LHRH analogue fusions suggests a means for providing fusion proteins comprising TraTp with other immunogenic epitopes, those epitopes including peptides of natural or synthetic origin, including fragments of proteins. The proteins may be hormones or growth factors such as LHRH, LH, FSH, chorionic gonadotrophin (CG), adrenocorticotrophic hormone (ACTH), somatotrophin, somatostatin, insulin-like growth factors, inhibin, activin, follistatin and variants thereof; they may be proteins of biological interest such as sperm antigens or ovum antigens such as zona pellucida antigens; alternatively, they may be antigens derived from parasite proteins, such parasites including protozoans, nematodes, cestodes, insects and ticks; they may also include antigens from bacteria or viruses, especially those protective against diseases in mammals, such diseases including cholera, AIDS, rabies, tetanus, smallpox, polio, diphtheria and others of commercial significance. It can be seen that in accordance with this invention fusion of TraTp and LHRH analogue sequences can be used to provide vaccines for immunising against LHRH and the present inventors believe that this approach could be extrapolated to the abovementioned further immunogenic epitopes on the basis of the teachings contained herein.

CLAIMS:

10. A vaccine according to claim 9 wherein the adjuvant is saponin.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw De

☐ 4. Document ID: US 5043267 A

L18: Entry 4 of 7 File: USPT Aug 27, 1991

DOCUMENT-IDENTIFIER: US 5043267 A
** See image for Certificate of Correction **
TITLE: Method for rapid detection of bacterial and fungal infection

Abstract Text (1):
A method for detecting pathogen infection in a host is provided. The method comprises lysing phagocytes from the host to release soluble components of the pathogen which are detected subsequently using a specific binding assay.

Brief Summary Text (2):
The present invention relates to a rapid method for diagnosing the etiologic agent of bacterial or fungal infections in a host. The method involves the disruption of phagocytes to release soluble components of phagocytosed pathogens for subsequent detection in a specific binding assay.

Brief Summary Text (4):
Diagnosis of infection frequently involves a determination of the causative pathogen. In the case of bacterial infection, a knowledge of the pathogen can lead to an informed choice of antibiotic.

Brief Summary Text (6):
By far, the most widely used method is culture, which involves inoculating a nutrient medium with a sample and then determining the extent of organism growth. Culture techniques are time consuming and are restricted in that they are capable of revealing the presence of only live organisms. Successful diagnosis relies upon selecting the appropriate culture media and conditions which will foster the growth of the etiologic agent. Fastidious organisms such as Mycoplasma spp., Neisseria spp., Haemophilus spp., and all obligate anaerobic organisms for example, require extraordinary culture conditions and extended periods of time to grow. If appropriate growth conditions are not met, these fastidious etiologic agents are likely to be missed when subjected to standard culture screening procedures.

Brief Summary Text (7):
Immunoassay, while promising the potential for rapidity of diagnosis, frequently lacks the sensitivity required to detect microorganisms which, during 30 to 50% of all septicemia, are present at less than or equal to one colony forming unit (CFU) per milli-liter of blood. [Kiehn, T. E. et al., J. Clin. Micro. 18, 300-304 (1983).]

Brief Summary Text (9):
It is known that phagocytes engulf numerous microbial pathogens. Some organisms reside within the phagocytes as intracellular parasites, while others are at a minimum, rendered nonviable by the internal degradative process of the phagocyte and, at a maximum, digested by these degradative processes.

Brief Summary Text (10):
Zierdt et al. have shown that lysis-filtration blood culture was a more sensitive culture technique than a non-lysis blood culture technique for the detection of pathogenic bacteria during septicemia in rabbits. The authors postulate that the lyses solution (a mixture of Tween-20 and Rhozyme) lyses phagocytes, thereby releasing engulfed pathogens whose viability has not been destroyed by the internal degradative processes of the phagocyte. These authors detected the presence of pathogens using conventional culture techniques. [Zierdt et al., J. Clin. Micro., 15, 74-77 (1982).] These conventional techniques can, however, only detect viable organisms not soluble products of phagocytic degradation.

Brief Summary Text (12):
While the lysing solution used by Zierdt et al. does lyse phagocytes to release viable pathogens for subsequent culturing, the presence of protease and nuclease in the lysing solution could present problems in other detection systems such as immunoassay or nucleic acid hybridization. It might be expected that these degradative enzymes would destroy the specific reagents required. Similarly, the

degradation enzymes of the phagocyte are also released by lysis and are another source of potential degradation of the specific detection reagents.

Brief Summary Text (13):
According to Zierdt et al., the release of viable pathogen from phagocytes is desirable because the total number of viable organisms available for growth in a culture-based detection system increases.

Brief Summary Text (15):
Friedlander, Infection and Immunity, Volume 22, 148-154 (1978), reports an assay for measurement of microbial killing by phagocytes. This method assumes that release of soluble radioactively labelled DNA from the microbe is direct evidence of cell death. As noted by Friedlander, since the standard assay condition did not include lysis of the phagocytes, all radioactivity detected must have been external to the phagocytes. When the phagocytes were lysed prior to testing for soluble radioactivity, no additional radioactivity was detected. This indicated that the soluble degraded DNA did not accumulate in the phagocytes, but rather was immediately released.

Brief Summary Text (16):
Richards et al., U.S. Pat. No. 4,581,331, issued Apr. 8, 1986, report a method for detection of virus or viral antigens by lysing phagocytes, separating the soluble fraction containing the virus or viral antigen and then detecting the virus or viral antigen. The only specific lytic agent reported is purified saponin. Detector systems reported include tissue culture, immunoassay and nucleic acid hybridization.

Brief Summary Text (17):
It has been found that phagocyte lysates yielding nonviable products of pathogens subjected to the internal degradative processes of the phagocytes can be used to advantage in clinical diagnosis if one uses an immunoassay or hybridization based pathogen detection system rather than a culture based detection system. The degradative processes of the phagocyte have been found in at least two examples not to degrade antigens to the point where they can no longer be recognized by their complementary antibodies.

Brief Summary Text (19):
The present invention is a method for detecting the presence of a bacterial or fungal pathogen in a host, which pathogen is phagocytosed and subject to at least partial degradation by phagocytes of the host, comprising:

Brief Summary Text (21):
(2) contacting the population with saponin capable of rupturing the phagocytes to release at least one soluble component of the pathogen, but incapable of rupturing unphagocytosed pathogen;

Brief Summary Text (22):
(3) separating at least one soluble component of the degraded pathogen from unphagocytosed pathogen;

Detailed Description Text (2):
The present invention is applicable for the diagnosis of many bacterial and fungal infections in man and other mammals. The method should be useful in both human and veterinary medicine. Bacteria and fungi which can be detected by the present method are those which are both phagocytosed and at least partially degraded in the phagocyte. Many clinically significant pathogens fall within this group. Generally, the gram positive and gram negative bacteria can be detected. Specifically, gram positive bacteria belonging to the genera Staphylococcus, Streptococcus, Listeria, Clostridium, and Corynebacteria can be detected. Gram negative bacteria belonging to the family Enterobacteriaceae can be detected. Gram negative bacteria belonging

to the genera Haemophilus, Bacteroides, Pseudomonas, Neisseria, and Legionella can be detected. Fungi belonging to the genera Candida, Cryptococcus, Coccidiodes and Histoplasma can be detected. Bacteria and fungi belonging to these various families and genera are known to be phagocytosed by phagocytes which comprise polymorphonuclear leukocytes (PMN), monocytes and tissue macrophages. With the passage of time, the pathogen is increasingly degraded by the phagolysosomal system. The degree and rate of phagolysosomal degradation varies depending upon the age of the organism and the nature of the pathogen. This degradative process causes the removal of characteristic surface structure com-ponents of the pathogen such as pili from Neisseria, capsular polysaccharides from Streptococcus pneumoniae, and lipoteichoic acid which is found in virtually all gram positive bacteria. As the degradative process continues, microbial cell wall and membrane integrity are altered by the action of PMN-specific degradative processes and microbial-specific autolysins. Once the innermost cell membrane is ruptured, intracellular components of the pathogen such as DNA and RNA will be released. Once those intracellular components are released, the degradative enzymes of the phagocyte begin to destroy those components also.

Detailed Description Text (4):
The cellular population is contacted with a lytic agent having the ability to rupture the phagocytes, but not having the ability to rupture unphagocytosed pathogen. In this way, the whole, viable pathogen, whether released from a PMN or free in the medium, will be available for culture-based detection to confirm the presumptive result of the more rapid soluble component-binding assay detection scheme of the present invention. Suitable lytic agents include Tween-20, a mild nonionic surfactant having an HLA index of less than 15, and the sapogenin glycosides particularly in purified form such as saponin, described by Dorn in U.S. Pat. No. 3,883,425, issued May 13, 1975, which is incorporated herein by reference. It is imperative that harsh treatments such as heat, proteolytic enzymes, strong reducing agents, strong acids and bases be avoided, in that they may not only kill viable pathogen, but may also denature the soluble pathogen components resulting from the phagocytic degradative process, making these components unrecognizable by their biospecific binding partners which include antibodies and nucleic acids.

Detailed Description Text (5):
The soluble pathogen components which result from phagocyte degradation of the intact pathogen include various chemical species which are unique to either the pathogen or a taxonomic group of which the pathogen is a member. Specific examples of soluble components and their relevance to diagnosis of microorganism presence appear in Table 1.

Detailed Description Text (6):
Soluble components can be operationally defined as those pathogen specific components which are not sedimented into a pellet fraction when subjected to a centrifugal field sufficient to pellet whole pathogens.

Detailed Description Text (11):
These surpirising advantages are a result of the process of this invention meeting the requirements that the organisms be rapidly inactivated (greater than 99% killing in two hours). the soluble components not be completely degraded rapidly, and that these components accumulate in the phagocytes to levels which can be detected by non-culture methods.

Detailed Description Text (12):
Because the present method disrupts phagocytes to release soluble pathogen components without affecting viability of unphagocytosed pathogen, a test sample can be separated, preferably by centrifugation, after the cell population is contacted with the lytic agent, into two phases: one containing insoluble, viable pathogen and the other containing soluble components. A fractional aliquot of each phase can then be tested. The soluble components can be detected in accordance with

the present invention, while the insoluble components (whole, viable pathogen) can be added to nutrient media which is examined for growth. In this way, the traditional culture-based technique can be used to confirm the more rapid technique which constitutes the present invention. Conveniently, separation into the two phases can be accomplished using the tube described by Dorn in U.S. Pat. No. 4,131,512, issued Dec. 26, 1978, which is sold by the Du Pont Company under the name ISOLATOR.TM..

Detailed Description Text (21):
A second 10 mL aliquot of blood was placed into the lysis-centrifugation device described in U.S. Pat. No. 4,131,512, issued to Dorn on Dec. 26, 1978. The blood sample was centrifuged, and the topmost 8.5 mL of supernatant fluid was removed and maintained at 4.degree. C. The remaining fluid, containing pelleted microorganisms, was vigorously agitated to produce a suspension referred to hereinafter as the microbial concentrate. Approximately 1 mL of the microbial concentrate was plated directly onto agar enriched growth medium. The remaining 0.5 mL of microbial concentrate was placed into 10 mL of buffered saline, and bacteria were centrifuged at 3000 rpm for fifteen minutes in a Du Pont Sorvall RT-6000 refrigerated centrifuge using an H-1000 rotor. The supernatant fluid was decanted and discarded. The pellet was tested for the presence of bacteria by the immunoassay formats described above and by light microscopy at 400.times. and 1000.times.. No bacteria were detected by any of the tests. However, after a twelve hour growth period, small colonies of bacteria were visible on the medium. The results were comparable to those obtained by broth culture. The 8.5 mL supernatant fluid described above was tested for the presence of bacteria. No bacteria were detected by either growth on nutrient medium or by direct microscopic examination. However, immunoassay was positive for peptidoglycan.

Detailed Description Paragraph Table (1):
TABLE 1 Chemical Composition of Gram-positive and Gram-negative Microorganisms.

Polymer	Gram+	Gram-
Peptidoglycan*	+	+
Teichoic acid* and/or teichuronic acid*	+	-
Lipopolysaccharide*	-	+
Lipoprotein	-	+
Phospholipid	-	+
Protein	+/-	+
Polysaccharide	+/-	-

*Macromolecules found only in prokaryotic organisms. [Ghuysen, JeanMarie, "Use of Bacteriolytic Enzymes in Determination of Wall Structure and their Role in Cell Metabolism" in Bacteriological Reviews 32:425-464, 1968.]-

CLAIMS:

1. A method for detecting the presence of a bacterial or fungal pathogen in a host, which pathogen is phagocytosed and subject to at least partial degradation by phagocytes of the host, comprising:

(1) isolating from the host a blood sample comprising a cellular population which comprises phagocytes;

(2) contacting the population with saponin capable of rupturing the phogocytes to release at least one soluble antibody of a phagocytosed bacterial or fungal pathogen but incapable of rupturing unphagocytosed pathogen;

(3) separating at least one soluble antibody of the degraded pathogen from unphagocytosed pathogen by centrifugation;

(4) contacting the soluble antibody in the supernatant fluid with a biospecific binding partner therefor; and

(5) measuring the extent of binding.

3. The method of claim 1 wherein the pathogen is Staphylococcus epidermidis, the

phagocyte is a polymorphonuclear leukocyte, the soluble antigen is peptidoglycan and the antibody is a monoclonal anti-peptidoglycan antibody.

4. The method of claim 1 wherein the pathogen is Streptococcus faecalis, the phagocyte is a polymorphonuclear leukocyte, the soluble component is lipoteichoic acid and the biospecific binding partner is a monoclonal anti-lipoteichoic antibody.

☐ 5. Document ID: US 4484923 A

L18: Entry 5 of 7 File: USPT Nov 27, 1984

DOCUMENT-IDENTIFIER: US 4484923 A
TITLE: Method for administering immunopotentiator

Brief Summary Text (21):
Further, in accord with the practice of the invention, the term immunopotentiator is used herein, generically embraces pharmaceutically acceptable and therapeutically acceptable naturally occurring and synthetic materials, representing, originating from, or simulating microorganisms, or their components, as well as materials of plant and animal origins, and their purified or simulated components, organic compounds, and inorganic compounds, that are capable of potentiating specific and non-specific immune response, increasing a host's resistance to an impending infection or disease in progress. The immunopotentiators possess pharmacological activity, that is, they are immunostimulatory agents that broadly enhance the immune response of a host leading to nonspecific immunity, for prophylaxis and defense, or they lead to the development of an increased specific immune response to an antigenic material already present in a host, for improved therapy in case of a preexisting disease.

Brief Summary Text (23):
More particularly, exemplary immunopotentiators that can be dispensed according to the practice of the invention, specifically include lipopolysaccharides (LPS) extracted from gram-negative bacteria such as Bordetella pertussia or Escherichia coli and the like, immunopotentiators obtained from anaerobic coryneforms, water soluble immunopotentiators obtained from the cell walls of bacteria especially from Calmette-Guerin bacillus, (BCG), immunopotentiators especially cord-factor extracted from mycobacteria, peptidoglycans, peptidoglycans containing an arabinoglactan, peptidoglycolipids containing alanine, glutamic and diamino pimelic acids, water-soluble immunopotentiators(WSA) isolated from cell walls and whole bacteria, e.g. of the species M. smegmatis, mucopeptides, immunopotentiators obtained from Bacillus subtilis, Saccharomyces cerevisiae, Listeria monocytogenes, Escherichia coli, immunopotentiating proteins of animal origin, immunopotentiating glycopeptides, N-acetylglucosamine derivatives, N-acetyl-muramyl-L-alanyl-D-isoglutamine, lipid A, lysolecithin analogues, polyanions, poly I:C, poly A:U, poly A, poly U, saponin, levamisole, tilorone, lentinan, thymic factor, lymphokines affecting cellular response only, immunopotentiators affecting humoral responses only, immunopotentiators affecting phagocytic response only, immunopotentiators affecting lymphocytic trapping only, nonimmunogenic immunopotentiators, and other immunopotentiators prepared synthetically or derived from the endocrine or derived from the lymphoid or from the reticuloendothelial systems, or otherwise found in animal organisms, and the like pharmaceutically acceptable immunopotentiators. The immunopotentiators are known to the art in Immunological Adjuvants, Report of WHO,

Geneva 1976, Biochemical and Biophysical Research Communications, Ellouz et al, Vol. 59, No. 4, pages 1317 to 1325, 1974; Agents and Actions, Bruley-Rosset et al, Vol. 6, pages 251 to 255, 1976; Chemical Abstracts, Vol. 88, 136982 to 136985, and 191481, 1978; Bibliotheca Tuberculosea, Freund, Fasc. 10, pages 130 to 148, 1956; The Antigens, Borek, Vol. 4, Chapter 6, pages 369 to 427, 1977; and the references cited therein.

Brief Summary Text (28):
The expression "a threat of impending infection" denotes an advancing or anticipated epidemic such as cholera, influenza, poliomyelitis, or rubella; childhood infections such as cytomegalovirus, measles, diptheria, poliomyelitis, mumps or rubella; infections prevalent in the environment into which the host is about to enter such as diseases of the tropics including typhoid, cholera, paratyphoid, shigellosis and malaria; infections to which the animal may have been accidentally exposed such as tetanus, rabies and gangrene; diseases such as pneumoccal pneumonia, pseudomonas and bacteroids infections, diseases caused by organisms found abundantly in the environment, but occuring mainly in compromised hosts, and the like. The expression "a disease in progress" denotes a disease such as herpes simplex, rabies, hepatitis, malaria, and the like.

Brief Summary Text (29):
The immunopotentiator composition can be administered in controlled and continuous dosage amounts for producing local and systemic response. The routes of administration include the conventional routes such as intramuscular, subcutaneous, ear intraperitoneal, nasal, ocular, vaginal, transdermal, and the alimentary tract including oral and ano-rectal admission. For preferential local response, the route of introduction can be preselected accordingly. For example, the oral route is indicated for animals including humans where the purpose is to specifically activate the gastrointestinal tract against the threat of diseases for which this is the major or exclusive route of infection, such as poliomyletitis, E. coli enteritis, salmonellosis, typhoid fever, shigellosis, cholera, coccidiosis, and similar diseases. The intramuscular route is indicated for animals threatened with exposure or previously exposed to diphtheria toxoid, tetanus influenza virus, hepatitis virus, herepes simplex virus, salmomella, rhino virus and the like, and in animals challenged with Newcastle disease virus, anaplasma, blackleg, and the like. Routes of administration and body passageways are disclosed in The Merck Veterinary Manual, 4th Edition, 1973; and in Topley and Wilson's Principles of Bacteriology and Immunology, Vols. I and II, 1975.

Brief Summary Text (34):
The immune response, its intensity and the extent thereof produced by the method of the invention can be ascertained by measuring antibodies in the plasma by standard techniques. Additional techniques that can be used for ascertaining the nature of the provoked response include measuring active physiological reactions, such as skin reactions following topical subdermal or intradermal antigen administration, and by measuring the degree of inhibition of toxic response. More pertinent measures for the purpose of this invention include phagocytic index, macrophage enzyme activity, concentration of complement factors, protection from experimental bacterial, viral, fungal and parasitic infections, and particulate clearance from blood. These techniques and other acceptable techniques are known to the art in Fundamentals of Immunology, by Weiser et al, 1972, published by Lea & Febiger; in Immunolgy by Bellanti, 1971, published by W. B. Saunders Co.; in Practical Immunology, by Hudson et al, 1976, published by Blackwell Scientific Publications; in Essential Immunology by Roitt, 1974, published by Blackwell Scientific Publications; Handbook of Experimental Immunology, by Weir, 1973, published by Blackwell Scientific Publications; and in The Macrophage, by Pearsall et al, 1970, published by Lea & Febiger Co.; which publications are incorporated herein by reference.

Detailed Description Text (10):

In this exampIe, the coadministration of the antigen tetanus toxoid and the immunopotentiator lipopolysaccharide administered for 4 weeks is compared with the results of single injection.

Detailed Description Text (11):
The assay of immunity was performed using the toxin challenge method as follows: graded doses of tetanus toxin diluted in PO.sub.4 buffered saline containing 0.25% bovine serum albumin, BSA, were injected in 0.5 ml volume into each mouse subcutaneously. The mice were Swiss-Webster, female, weighing about 26 g. Mice were observed for symptoms of Tetanus, and death times were recorded. The periods of observation were as follows: 30-40 hours every 2 hours, 40-66 hours for every four hours, and 84 to 200 hours every 24 hours. The immunity was expressed as the number of minimum lethal doses of toxin required to kill immunized mice. The minimum lethal dose, MLD, is defined as the minimum dose of Toxin which kills all challenged mice in 200 hours or less.

Detailed Description Text (12):
The antitoxin titration was performed as follows: equal volumes of toxin and doubling dilution of antisera were mixed, incubated at 37.degree. C. for 1 hr. and injected subcutaneously in 0.5 ml volume into normal mice. Three mice were tested at each dilution of antiserum. The potency of the test sera were assayed in comparison with the standard tetanus antitoxin, tested in parallel with the test sera. The antitoxin titrations were carried out at 1+/400 levels, that is, the dose of toxin injected into each mouse was such that when mixed with 1/400 units of the standard antitoxin, the mixture killed the mice in 168 hours.

Detailed Description Text (13):
The experiment compares the immunopotentiating effect of lipopolysaccharide given simultaneously with antigen in a single injection with the immunopotentiating effect of lipopolysaccharide given simultaneously and continuously with antigen for four weeks. The antigen used, tetanus toxoid, permitted the use of an in vivo assay, with neutralization of toxin, for measuring the immunopotentiating effect.

Detailed Description Text (14):
Nine groups of mice (7/group) were immunized with a constant dose of tetanus toxoid (0.1 Lf=0.3 g) mixed with graded doses of LPS. Five of the groups received the immunizing dose of LPS and antigen, or antigen alone by a single subcutaneous injection. The immunizing dose was administered to the other 4 groups for 4 weeks, 4W. Twenty-eight days after the initiation of immunization, all mice were bled for antitoxin titration. On day 33, 3 mice from each group were challenged with 20 or 50 minimum lethal doses of tetanus toxin, and on day 35, the remaining 4 mice from each group were challenged with 8, 20, 50 or 125 MLDs. The results for the immunopotentiating effect of continuous administration of tetanus toxoid with or without lipopolysaccharide are given in TABLE II.

Detailed Description Text (20):
Three groups of Swiss-Webster mice, 10 per group, were used in the study. Groups I and II were immunized with tetanus toxoid, with or without LPS, lipopolysaccharide adminstered in two tiers. In group I, the first tier was administered, without LPS, via a single subcutaneous injection on day zero, in group II, the first tier was administered with LPS via a continuous delivery miniature pump over a period of 3 days. The mice in group III were immunized with tetanus toxoid and LPS administered continuously through a 4 week miniature pump. In this experiment, therefore, a single tier administration is applied.

Detailed Description Text (22):
On day 39-41, mice in groups of 3-4 were challenged with 125, 250 and 500 MLDs of tetanus toxin.

CLAIMS:

1. A method for potentiating the immune response of a host, which method consists essentially of administering to a host having an immune system and needing potentiation of its immune response, an immunopotentiating agent that is a member selected from the group consisting of an immunopotentiating lipid, immunopotentiating levamisole, immunopotentiating cord factor, immunopotentiating tilorane, immunopotentiating saponin, immunopotentiators prepared synthetically and derived from the endocrine system, immunopotentiators prepared synthetically and derived from the lymph system and immunopotentiators prepared synthetically and derived from the reticuloendothelial system, and wherein said agent is administered from a therapeutic delivery system that limits the contact of the host with the agent until the agent is released from the system, thereby lessening the incidence of local inflammation, fever and adverse biological response of the host to the agent, which agent is administered at a controlled rate and continously in a therapeutically effective amount of at least one picogram for a prolonged period of time for potentiating the immune response.

☐ 6. Document ID: US 4053363 A

L18: Entry 6 of 7 File: USPT Oct 11, 1977

DOCUMENT-IDENTIFIER: US 4053363 A
**** See image for Certificate of Correction ****
TITLE: Sputum analysis method

Abstract Text (1):
An in vitro diagnostic technique for quantitative analysis of human sputum, such as lung fluid, for the presence of microbial pathogens is provided wherein a sputum sample is contacted with a minor quantity of nontoxic saponin to degrade the viscosity of the sputum and thereafter the sputum is thoroughly admixed to distribute microbial pathogens generally uniformly therein. The sputum can be diluted as desired and then subjected to conventional analytical techniques, i.e., plating on growth media and recording results.

Brief Summary Text (2):
This invention relates to the quantitative analysis of human sputums for the presence of microbial pathogens. In another aspect, this invention relates to a novel technique of liquefying sputum specimens with a saponin mucolytic agent.

Brief Summary Text (3):
The condition of pneumonia in a human patient generally comprises an acute inflammatory condition of a lung or lungs which can be caused by microbial pathogens such as bacteria or viruses as well as chemical irritants or foreign bodies. In order to determine the causal agent in a patient with a presumptive diagnosis of pneumonia, samples of lung fluid are required. The ideal specimens of lung fluid are homogeneous samples which can be obtained by surgical intervention, for example, transtrachael aspiration. As is typical, surgical intervention techniques are time consuming and present a risk to the patient. Fatal reactions have been reported resulting from transtrachael aspiration. For example, hypotoxic patients and those suffering from debilitating diseases such as blood dyscrasia are especially prone to serious complications from transtrachael aspiration.

4 ANSWER 4 OF 41 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:52050 CAPLUS <<LOGINID::20070426>>
DOCUMENT NUMBER: 118:52050
ENTRY DATE: Entered STN: 16 Feb 1993
TITLE: Immunogenicity and toxicity testing of an experimental HIV-1 vaccine in nonhuman primates
AUTHOR(S): Newman, Mark J.; Wu, Jia Yan; Coughlin, Richard T.; Murphy, Cheryl I.; Seals, Jonathan R.; Wyand, Michael S.; Kensil, Charlotte R.
CORPORATE SOURCE: Cambridge Biotech Corp., Worcester, MA, 01605, USA
SOURCE: AIDS Research and Human Retroviruses (1992), 8(8), 1413-18
CODEN: ARHRE7; ISSN: 0889-2229
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 1-7 (Pharmacology)
ABSTRACT:
A highly purified saponin from Quillaja saponaria (QS-21) was tested in juvenile rhesus macaques for adjuvant activity and toxicity. The QS-21 was tested alone or as part of an exptl. subunit HIV-1 vaccine containing a truncated recombinant HIV-1 envelope protein (gp 160D) adsorbed to alum. No toxic effects were observed, even after the administration of the exptl. vaccines three times at monthly intervals. The QS-21 saponin adjuvant enhanced total antibody production levels by greater than 100-fold and broadened the specificity of the response so that addnl. epitopes were recognized, when compared with alum-adsorbed HIV-1 gp160D formulation. Low-level, antigen-specific proliferative responses to HIV-1 recombinant gp160 were induced by either vaccine formulation. Proliferative responses were induced by a sham challenge with soluble recombinant HIV-1 gp160 for all of the animals that has been vaccinated. However, those that received the HIV-complete vaccine formulation containing QS-21 responded significantly better. These data demonstrated that the QS-21 adjuvant augmented both antibody responses and cell-mediated immunity and established immunol. memory. The potent adjuvant activity and lack of toxicity suggest that this ***adjuvant*** should be safe and effective for use in HIV-1 vaccines.

L4 ANSWER 5 OF 41 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1992:631765 CAPLUS <<LOGINID::20070426>>
DOCUMENT NUMBER: 117:231765
ENTRY DATE: Entered STN: 13 Dec 1992
TITLE: QS-21 augments the antibody response to a synthetic peptide vaccine compared to alum
AUTHOR(S): Kirkley, J. E.; Naylor, Paul H.; Marciani, Dante J.; Kensil, Charlotte R.; Newman, Mark; Goldstein, A. L.
CORPORATE SOURCE: Dep. Biochem. Mol. Biol., George Washington Univ. Med. Cent., Washington, DC, USA
SOURCE: Comb. Ther., [Proc. Int. Symp.], 1st (1992), Meeting Date 1991, 231-6. Editor(s): Goldstein, Allan L.; Garaci, Enrico. Plenum: New York, N. Y. CODEN: 58FMAC
DOCUMENT TYPE: Conference
LANGUAGE: English
CLASSIFICATION: 15-2 (Immunochemistry)
Section cross-reference(s): 63

ABSTRACT:
Saponin QS-21 was a more potent adjuvant than alum when the antibody response to either the peptide hapten, HGP-30 (a synthetic peptide from amino acid residues 85-114 near the C-terminal of HIV-1 virus p17 gag protein), or the carrier, keyhole limpet hemocyanin was examined QS-21 was well tolerated by the immunized mice. There were no differences in reactions at the injection site between QS-21, QS-21 plus alum, and alum alone. While the addition of alum to QS-21 modestly augmented the antipeptide titer, it did not have a sizeable effect on the response generated by QS-21, nor did it neg. affect the adjuvant activity of the stronger QS-21.

copies, i.e. as multimers.

Brief Summary Text (12):
For such viruses it is more practical to inject them together with the new adjuvant complex than to couple hydrophobic groups to them or create hydrophobic groups by other means (e.g. partial denaturation) and integrate them into an iscom particle.

Brief Summary Text (64):
A matrix containing a sterol such as cholesterol, saponins, adjuvants and optionally further lipids can be used as an adjuvant. It can be used for potentiating the antigenic effect of any antigen or antigenic determinants from any pathogenic organism or any fragments or subunits of, or derived from these. Thus it can be used as an adjuvant for those antigens that are integrated in an iscom. Such antigens are mentioned in the EPC-patent applications 83850273.0 and 85850326.1, which are hereby incorporated as references. Thus the matrix can be used as adjuvants together with antigens or antigenic determinants derived from viruses with or without envelope, bacteria, protozoa, mycoplasmas, helminths, mollusca or together with such whole organisms. The antigenes or antigenic determinants might further be hormones, enzymes, carbohydrates and carbohydrate-containing structures such as lipopolysaccharides, peptides or proteins or recombinants thereof.

Brief Summary Text (71):
Mice were immunized with envelope protein from influenza virus in the form of iscom complex, micelles and micelles together with the new complex according to the invention (so called matrix). The immune response was evaluated by measuring the antibodies with ELISA technique 15, 30, 44 and 50 days after injection. The following injections were made:

Brief Summary Text (86):
One can conclude that envelope protein from influenza virus in the form of iscom or micelles plus the adjuvant complex (matrix) according to the invention gives the highest antibody titres. The dose of matrix can be kept very low, i.e. 0.1 .mu.g, and still has a notable adjuvant effect.

Brief Summary Text (87):
3. Comparison between the immunogenic effects from diphtheria toxoid (DT) in monomeric form, monomeric DT+iscom containing envelope protein from influenza virus, monomeric DT in mixture with Quil A and cholesterol and monomeric DT+adjuvant complex (matrix) according to the invention.

CLAIMS:

1. A vaccine comprising an immunomodulating agent having an iscom-like structure and comprising within said iscom-like structure at least one lipid and at least one saponin, said iscom-like structure being free of incorporated antigens; one or more antigens in admixture with said immunomodulating agent but not integrated into said iscom-like structure; and a pharmaceutically acceptable vehicle.

2. A kit for human or veterinary medical use, comprising: (a) an immunomodulating agent having an iscom-like structure and comprising within said iscom-like structure at least one lipid and at least one saponin, said iscom-like structure being free of incorporated antigens; and (b) one or more immunomodulating substances and a pharmaceutically acceptable vehicle; said components (a) and (b) being confined in separate containers.

3. A method of inducing an immunomodulatory response in a patient in need thereof, comprising administering (a) an antigenically effective amount of at least one antigen, and (b) an immunomodulating agent in an amount effective to produce an immunomodulatory effect on the action of said at least one antigen, said immunomodulating agent having an iscom-like structure and comprising within said

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☐ 1. Document ID: US 5679354 A

L18: Entry 1 of 7 File: USPT Oct 21, 1997

DOCUMENT-IDENTIFIER: US 5679354 A
TITLE: Matrix with immunomodulating activity

Abstract Text (1):
The invention claims an iscom matrix which is not a lipid vesicle comprising at least one lipid and at least one saponim but no intentional antigenic determinants and optionally also adjuvants for use as an immunomodulating agent, medicines, vaccines, kits containing the matrix and new saponins, and a process for preparing the new saponins. The invention also concerns a process for preparing the matrix characterized in that at least one sterol is solubilized in a solvent or detergent, the saponin or saponins are added, the other adjuvants and lipids are optionally also added, whereafter the organic solvent or the detergent may be removed for example with dialysis, ultra filtration, gel filtration or electrophoresis. The sterol and saponin might also be solubilized in the lipids and/or adjuvants.

Brief Summary Text (2):
Many microbial and vital antigens can be produced by modern techniques today. Their full promise in vaccines will however not be realized unless they are administered along with an effective adjuvant, an agent that increases antibody and/or cell-mediated immune responses.

Brief Summary Text (3):
The only adjuvants currently authorized for human use in most countries are aluminum hydroxide and aluminum phosphate which have been used for many years to increase antibody responses to e.g. diphtheria and tetanus toxoids. Although these adjuvants are sufficient for many vaccines, studies have shown that other adjuvants, e.g. Freund's complete adjuvant (FCA), and Quil A often are more efficacious in eliciting antibody response and cell-mediated immunity in experimental animals. In fact, they are frequently required for protection. However. FCA produces granulomas at injection sites, which makes them unacceptable for human and veterinary vaccines. In fact, even aluminum hydroxide may give rise to reactions in form of granuloma at the injection site. For these reasons, many attempts are made to develop adjuvants with the efficacy of FCA but without undesirable side effects.

Brief Summary Text (11):
When an adjuvant is used in a matrix according to the invention, the antigen is not integrated in the same particle as the adjuvant as is done in an iscom particle according to the above mentioned EPC Patent Applications. This implies that one can use antigens without amphiphatic properties or antigens which can not be forced to expose hydrophobic regions. As an example it can be mentioned that some viruses do not have amphiphatic proteins, e.g. picornavirus, adenovirus or parvovirus, but they have a form of submicroscopic particle with the antigen presented in several

L2: Entry 2 of 128 File: USPT Aug 27, 2002

DOCUMENT-IDENTIFIER: US 6440416 B1
TITLE: Vaccines against cancer and infectious diseases

Application Filing Year (1):
1992

Brief Summary Text (52):
In order to overcome the weak immunogenicity of primate anti-idiotype antibodies or fragments, especially baboon Ab2.beta., in human recipients, the immunoglobulins are preferably made more immunogenic by administration in a vaccination vehicle. Typically, they are injected in combination with an adjuvant such as Freund's complete or incomplete adjuvant, alum, or the like. Furthermore, their immunogenicity can be increased by coupling to an immunogenic carrier known to be safe in humans, e.g., an attenuated microbial agent such as tetanus toxoid, Bacillus Calmette-Guerin (BCG) or the like.

CLAIMS:

12. The method of claim 11, wherein said adjuvant is at least one member selected from the group consisting of Freund's adjuvant, alum, Bacillus Calmette-Guerin and tetanus toxoid.

22. The vaccine of claim 21, wherein said adjuvant is at least one member selected from the group consisting of Freund's adjuvant, alum, Bacillus Calmette-Guerin and tetanus toxoid.

L2: Entry 128 of 128 File: USPT Nov 11, 1975

DOCUMENT-IDENTIFIER: US 3919411 A
TITLE: Injectable adjuvant and compositions including such adjuvant

Application Filing Year (1):
1974

Brief Summary Text (31):
Many types of medicinal agents may be incorporated with the adjuvant of this invention. In the antigen category, exemplary active immunogenic agents include Clostridium Chauvoei; Clostridium septicum; Erysipelothrix insidious; Leptospiria anterogens; Streptoccus equi; Clostridium sordellia; Clostridium novyi; and Clostridium hemolyticum. Toxoid antigens which can be combined with the adjuvant include Clostridium perfringens (Types C and D); and Clostridium tetani. Viral type antigens include Encephalomyelitis (WEE and EEE); Foot Mouth Disease Virus FMVD); Encephalomyelitis (WEE), Encephalomyelitis (EEE) and Clostridium tetani in combination; Bovine virus diahrrea (BVD); Infectious bovine rhinotracheaitis (IBR); Parainfluenza (PI.sub.3); and measles virus. Usable serums include tetanus antiserum, and Clostridium perfringens (Types B, C and D) in serum form. Adrenalin is one of a number of hormones which may be combined with the adjuvant system previously described.

Detailed Description Text (82):
A known antigenic strain of clostridium tetanus was grown, inactivated and purified according to conventional standard procedures. Nine experimental toxoids were prepared from a common batch for use with the adjuvants described below.

Detailed Description Text (86):
Adjuvant-Toxoids were prepared by admixing 15 ml. of inactivated tetanus toxoid containing 200 LF/ml to 10 ml. of a given emulsion, 0.25 grams Carbopol 934P, followed by addition of qs. to 100 ml. with sterile water. The constituents of the adjuvant-toxoid systems tested are tabulated below:

Detailed Description Text (88):
Groups of five guinea pigs (each pig weighing about 500 grams) were innoculated with 0.4 ml. each of the adjuvant-antigens and controls listed above. Six weeks after inoculation, all guinea pigs were bled by cardiac puncture and equal volumes of serum from each pooled. The pooled serum from each group was diluted 1:20, 1:40, 1:60, 1:80 and 1:100. Three ml. of each dilution was combined with 6 ml. of standard tetanus toxin which contains one test dose per two ml. The toxin-serum mixtures were held for one hour at room temperature to allow neutralization of the toxin to take place.

Previous Doc Next Doc Go to Doc#

L2: Entry 128 of 128 File: USPT Nov 11, 1975

DOCUMENT-IDENTIFIER: US 3919411 A
TITLE: Injectable adjuvant and compositions including such adjuvant

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1974

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Previous Doc Next Doc Go to Doc#

iscom-like structure at least one lipid and at least one saponin, said iscom-like structure being free of incorporated antigens; said components (a) and (b) being administered in admixture, or separately.

7. The method according to claim 3, wherein said at least one saponin is a triterpensaponin.

9. A kit for human or veterinary medical use, comprising: (a) an immunomodulating agent having an iscom-like structure and comprising within said iscom-like structure at least one lipid and at least one saponin, said iscom-like structure being free of incorporated antigens; and (b) one or more immunomodulating substances and a pharmaceutically acceptable vehicle; said components (a) and (b) being in admixture in a single container.

10. The vaccine according to claim 16, wherein said saponin is isolated from Quillaja Saponaria Molina of .beta.-amyrin type with 8-11 carbohydrate moieties, and is selected from the group consisting of:

a) substance B2 having a molecular weight of 1988, a carbon 13 NMR spectrum as shown in FIGS. 5A and 6A, and a proton NMR spectrum as shown in FIGS. 11A and 12A;

b) substance B3 having a molecular weight of 2150 and a carbon 13 NMR spectrum as shown in FIGS. 5B and 6B, and a proton NMR spectrum as shown in FIGS. 11B and 12B; and

c) substance B4B having a molecular weight of 1862, a carbon 13 NMR spectrum as shown in FIGS. 5C and 6C, and a proton NMR structure as shown in FIGS. 11C and 12C.

☐ 2. Document ID: US 5583112 A

L18: Entry 2 of 7 File: USPT Dec 10, 1996

DOCUMENT-IDENTIFIER: US 5583112 A
TITLE: Saponin-antigen conjugates and the use thereof

Abstract Text (1):
Saponin/antigen conjugates and the use thereof for enhancing immune responses in individuals are disclosed. The saponins may be substantially pure or mixtures of saponins.

Detailed Description Text (30):
Among the saponin mixtures effective in the present invention are fractions QA-7 and QA-17, QA-7 and QA-18, QA-17 and QA-18, or QA-7, QA-17, and QA-18 administered together. Purified saponins and conjugates thereof may also be administered together with non-saponin adjuvants. Such non-saponin adjuvants useful with the present invention are oil adjuvants (for example, Freund's Complete and Incomplete), liposomes, mineral salts (for example, AlK(SO.sub.4).sub.2, AlNa (SO.sub.4).sub.2, AlNH.sub.4 (SO.sub.4), silica, alum, Al(OH).sub.3, Ca.sub.3 (PO.sub.4).sub.2, kaolin, and carbon), polynucleotides (for example, poly IC and poly AU acids), and certain natural substances (for example, wax D from Mycobacterium tuberculosis, as well as substances found in Corynebacterium parvum, Bordetella pertussis, and members of the genus Brucella), bovine serum albumin,

diphtheria toxoid, tetanus toxoid, edestin, keyhole-limpet hemocyanin, Pseudomonal Toxin A, choleragenoid, cholera toxin, pertussis toxin, viral proteins, and eukaryotic proteins such as interferons, interleukins, or tumor necrosis factor. Such proteins may be obtained frown natural or recombinant sources according to methods known to those skilled in the art. When obtained from recombinant sources, the non-saponin adjuvant may comprise a protein fragment comprising at least the immunogenic portion of the molecule. Other known immunogenic macromolecules which may be used in the practice of the invention include, but are not limited to, polysaccharides, tRNA, nomnetabolizable synthetic polymers such as polyvinylamine, polymethacrylic acid polyvinylpyrrolidone, mixed polycondensates (with relatively high molecular weight) of 4'4'-diaminodiphenyl-methane-3,3'-dicarboxylic acid and 4-nitro-2-aminobenzoic acid (See Sela, M., Science 166:1365-1374 (1969)) or glycolipids, lipids or carbohydrates.

Detailed Description Text (39):
The saponins of the present invention may be utilized to enhance the immune response to any antigen. Typical antigens suitable for the immune-response provoking compositions of the present invention include antigens derived from any of the following: viruses, such as influenza, feline leukemia virus, feline immunodeficiency virus, HIV-1, HIV-2, rabies, measles, hepatitis B, or hoof and mouth disease; bacteria, such as anthrax, diphtheria, Lyme disease, or tuberculosis; or protozoans, such as Babeosis bovis or Plasmodium. The antigens may be proteins, peptides or polysaccharides. The proteins and peptides may be purified from a natural source, synthesized by means of solid phase synthesis, or may be obtained means of recombinant genetics.

Detailed Description Text (130):
Anti-FEA antibody was assayed by an ELISA assay. FEA virus (10 .mu.g/ml in PBS) was absorbed to Immulon II plates overnight at 4.degree. C. (100 .mu.l/well). The plates were washed with PBS and nonspecific antibody binding was blocked by incubation for 1 hour with 10% normal goat serum in PBS (100 .mu.l/well) at room temperature. Plates were then washed with 0.05% Tween-20 in distilled water. Sera was diluted in 10% normal goat serum in PBS and incubated for 1 hour at room temperature on the plate at serum dilutions of 10, 10.sup.2, 10.sup.3, and 10.sup.4 (100 .mu.l/well). After washing the plates with 0.05% Tween-20 in distilled water, they were incubated for 30 minutes at room temperature with 100 .mu.l/well of peroxidase-conjugated goat anti-mouse IgG (Boehringer-Mannheim) diluted 1/5000 in PBS. After washing the plates with 0.05% Tween-20 in distilled water, the amount of IgG-binding was determined by peroxidase reaction with 3,3',5,5'-tetramethylbenzidine from the absorbance at 450 nm determined on a Dynatech microtiter plate reader.

Detailed Description Text (133):
CD-1 mice (8-10 weeks old) were immunized intradermally with 15 .mu.g/dose of alkylated gp70R-delta purified by procedure II of Example 13 (absorbed to aluminum hydroxide as described in Example 14) in 200 ul PBS. HPLC-purified adjuvants QA-7, QA-17, QA-18 and mixtures of the three adjuvants were used at a dry weight dose of 10 .mu.g. Three mice were injected for each formulation. Mouse sera was analyzed by ELISA at 2 and 4 weeks post-immunization for reactivity to FEA as described in Example 14. As with immunization with unmodified gp70R-delta shown in Example 12, immunization with alkylated gp70R-delta elicits an antiFeLV viral response by four weeks post-immunization. HPLC-purified adjuvants QA-7, QA-17, QA-18 all increase the immune response as compared to immunization in the absence of the saponin adjuvants. QA-17 and mixtures of QA-17 and QA-18 induced the highest response, inducing endpoint titers almost two orders of magnitude greater than immunization in the absence of saponin adjuvants. The results of these experiments are summarized on FIGS. 17A-17B.

Other Reference Publication (1):
Berezin, V. E. et al., "Controlled Organization of Multimolecular Complexes of

Enveloped Virus Glycoproteins: Study of Immunogenicity", Vaccine 6:450-456 (1988).

Other Reference Publication (2):
Ert urk, M. et al., "Antibody Responses and Protection In Mice Immunized with Herpes Simplex Virus Type 1 Antigen Immune-Stimulating Complex Preparations", J. gen. Virol. 70:2149-2155 (1989).

Other Reference Publication (3):
Howard, C. R. et al., "Preparation and Properties of Immune-Stimulating Complexes Containing Hepatitis B. Virus Surface Antigen", J. gen. Virol. 68:2281-2289 (1987).

Other Reference Publication (28):
Osterhaus, Albert et al., "Induction of Protective Immune Response in Cats by Vaccination with Feline Leukemia Virus Iscom", J. Immunology 135: 591-596 (1985).

CLAIMS:

1. A saponin/antigen covalent conjugate composition or a saponin alkaline hydrolysis product/antigen covalent conjugate composition comprising a substantially pure saponin selected from the group consisting of QA-21-V1 and QA-21-V2, or an alkaline hydrolysis product of a substantially pure saponin selected from the group consisting of QA-21-V1 and QA-21-V2, wherein said saponin or saponin alkaline hydrolysis product comprises a glucuronate carboxyl group, said saponin or said saponin alkaline hydrolysis product being linked at the glucuronate carboxyl group to an antigen either directly or through a linker group, wherein the linkage does not interfere with the ability of said substantially pure saponin or said alkaline hydrolysis product to stimulate an immune response in an animal.

2. The saponin/antigen covalent conjugate of claim 1, wherein said linker group is a bifunctional molecule.

3. The saponin/antigen covalent conjugate of claim 1, wherein said linker group is selected from the group consisting of: ##STR2## wherein R" is hydrogen, C.sub.1-4 alkyl, or C.sub.1-4 alkyl substituted by phenyl, hydroxyphenyl, indolyl, mercapto, C.sub.1-4 alkylthio, hydroxy, carboxy, amino, guanidino, imidazolyl or carbamyl; or wherein R and R" together form a pyrrolidinyl or piperidinyl ring.

4. The saponin/antigen covalent conjugate of claim 1, wherein said substantially pure saponin is QA-21-V1, which has a retention time of approximately 6.4 minutes on HILIC on a PolyLC PHEA column having 5 .mu.m particle size, 4.6 mm ID.times.200 mm L in a solvent of 10 mM TEAP, pH 6.0, in water/acetonitrile (15/85%, v/v) at a flow rate of 1 ml/min.

5. The saponin/antigen covalent conjugate of claim 4, wherein said saponin contains about 22% carbohydrate per dry weight, and wherein said carbohydrate has a composition consisting of the following monosaccharides: terminal arabinose, terminal apiose, terminal xylose, 4-rhamnose, terminal galactose, 2-fucose, 3-xylose, and 2,3-glucuronic acid.

6. The saponin/antigen covalent conjugate of claim 1, wherein said substantially pure saponin is QA-21-V2, which has a retention time of approximately 6.9 minutes on HILIC on a PolyLC PHEA column having 5 .mu.m particle size, 4.6 mm ID.times.200 mm L in a solvent of 10 mM TEAP, pH 6.0, in water/acetonitrile (15/85%, v/v) at a flow rate of 1 ml/min.

7. The saponin/antigen covalent conjugate of claim 6, wherein said saponin contains about 22% carbohydrate per dry weight, and wherein said carbohydrate has a composition consisting of the following monosaccharides: terminal arabinose, two terminal xyloses, 4-rhamnose, terminal galactose, 2-fucose, 3-xylose, and 2,3-

glucuronic acid.

8. A vaccine which comprises a saponin/antigen covalent conjugate composition or a saponin alkaline hydrolysis product/antigen covalent conjugate composition and a pharmaceutically acceptable carrier, wherein said conjugate comprises a substantially pure saponin selected from the group consisting of QA-21-V1 and QA-21-V2, or an alkaline hydrolysis product of a substantially pure saponin selected from the group consisting of QA-21-V1 and QA-21-V2, wherein said saponin or saponin alkaline hydrolysis product comprises a glucuronate carboxyl group, said saponin or said saponin alkaline hydrolysis product being linked at the glucuronate carboxyl group to an antigen either directly or through a linker group, wherein the linkage does not interfere with the ability of said substantially pure saponin or said alkaline hydrolysis product to stimulate an immune response in an animal.

11. The vaccine of claim 8, wherein said substantially pure saponin is QA-21-V1, which has a retention time of approximately 6.4 minutes on HILIC on a PolyLC PHEA column having 5 .mu.m particle size, 4.6 mm ID.times.200 mm L in a solvent of 10 mM TEAP, pH 6.0, in water/acetonitrile (15/85 %, v/v) at a flow rate of 1 ml/min.

12. The vaccine of claim 11, wherein said saponin contains about 22% carbohydrate per dry weight, and wherein said carbohydrate has a composition consisting of the following monosaccharides: terminal arabinose, terminal apiose, terminal xylose, 4-rhamnose, terminal galactose, 2-fucose, 3-xylose, and 2,3-glucuronic acid.

13. The vaccine of claim 8, wherein said substantially pure saponin is QA-21-V2, which has a retention time of approximately 6.9 minutes on HILIC on a PolyLC PHEA column having 5 .mu.m particle size, 4.6 mm ID.times.200 mm L in a solvent of 10 mM TEAP, pH 6.0, in water/acetonitrile (15/85 %, v/v) at a flow rate of 1 ml/min.

14. The vaccine of claim 13, wherein said saponin contains about 22% carbohydrate per dry weight, and wherein said carbohydrate has a composition consisting of the following monosaccharides: terminal arabinose, two terminal xyloses, 4-rhamnose, terminal galactose, 2-fucose, 3-xylose, and 2,3-glucuronic acid.

16. The vaccine of claim 15, wherein said adjuvant is a saponin.

17. A method of enhancing an immune response to an antigen in an individual comprising administration of an effective amount of a saponin/antigen covalent conjugate composition or a saponin alkaline hydrolysis product/antigen covalent conjugate composition and a pharmaceutically acceptable carrier, wherein said conjugate comprises a substantially pure saponin selected from the group consisting of QA-21-V1 and QA-21-V2, or an alkaline hydrolysis product of a substantially pure saponin selected from the group consisting of QA-21-V1 and QA-21-V2, wherein said saponin or saponin alkaline hydrolysis product comprises a glucuronate carboxyl group, said saponin or said saponin alkaline hydrolysis product being linked at the glucuronate carboxyl group to an antigen either directly or through a linker group, wherein the linkage does not interfere with the ability of said substantially pure saponin or said alkaline hydrolysis product to stimulate an immune response in an animal.

20. The method of claim 17, wherein said substantially pure saponin is QA-21-V1, which has a retention time of approximately 6.4 minutes on HILIC on a PolyLC PHEA column having 5 .mu.m particle size, 4.6 mm ID.times.200 mm L in a solvent of 10 mM TEAP, pH 6.0, in water/acetonitrile (15/85 %, v/v) at a flow rate of 1 ml/min.

21. The method of claim 20, wherein said saponin contains about 22% carbohydrate per dry weight, and wherein said carbohydrate has a composition consisting of the following monosaccharides: terminal arabinose, terminal apiose, terminal xylose, 4-rhamnose, terminal galactose, 2-fucose, 3-xylose, and 2,3-glucuronic acid.

22. The method of claim 17, wherein said substantially pure saponin is QA-21-V2, which has a retention time of approximately 6.9 minutes on HILIC on a PolyLC PHEA column having 5 .mu.m particle size, 4.6 mm ID.times.200 mm L in a solvent of 10 mM TEAP, pH 6.0, in water/acetonitrile (15/85 %, v/v) at a flow rate of 1 ml/min.

23. The method of claim 22, wherein said saponin contains about 22% carbohydrate per dry weight, and wherein said carbohydrate has a composition consisting of the following monosaccharides: terminal arabinose, two terminal xyloses, 4-rhamnose, terminal galactose, 2-fucose, 3-xylose, and 2,3-glucuronic acid.

25. The method of claim 24, wherein said adjuvant is a saponin.

28. Substantially pure QA-21-V 1 saponin, wherein said pure saponin is characterized by a peak at 6.4 minutes on HILIC on a PolyLC PHEA column having 5 .mu.m particle size, 4.6 mm ID.times.200 mm L in a solvent of 10 mM TEAP, pH 6.0, in water/acetonitrile (15/85 %, v/v) at a flow rate of 1 ml/min.

29. The substantially pure QA-21-V 1 saponin of claim 28, wherein said saponin contains about 22% carbohydrate per dry weight, and wherein said carbohydrate has a composition consisting of the following monosaccharides: terminal arabinose, terminal apiose, terminal xylose, 4-rhamnose, terminal galactose, 2-fucose, 3-xylose, and 2,3-glucuronic acid.

30. Substantially pure QA-21-V2 saponin, wherein said pure saponin is characterized by a peak at 6.9 minutes on HILIC on a PolyLC PHEA column having 5 .mu.m particle size, 4.6 mm ID.times.200 mm L in a solvent of 10 mM TEAP, pH 6.0, in water/acetonitrile (15/85 %, v/v) at a flow rate of 1 ml/min.

31. The substantially pure QA-21-V2 saponin of claim 30, wherein said saponin contains about 22% carbohydrate per dry weight, and wherein said carbohydrate has a composition consisting of the following monosaccharides: terminal arabinose, two terminal xyloses, 4-rhamnose, terminal galactose, 2-fucose, 3-xylose, and 2,3-glucuronic acid.

32. A method of enhancing an immune response to an antigen in an individual comprising administration of the substantially pure saponin adjuvant of any one of claims 28-31 and an immunologically effective amount of an antigen to said individual in an amount sufficient to enhance the immune response of said individual to said antigen.

33. A pharmaceutical composition useful for inducing the production of antibodies to an antigen in an individual comprising an immunogenically effective amount of an antigen and at least one substantially pure saponin of any one of claims 28-31, wherein said substantially pure saponin is present in an amount sufficient to enhance the immune response of said individual to said antigen.

35. A substantially pure modified saponin comprising:

1) a saponin selected from the group consisting of QA-21-V 1 and QA-2 1-V2, wherein said saponin comprises a glucuronate carboxyl group; and

2) a linking group or blocking group covalently attached at said glucuronate carboxyl group,

wherein said substantially pure modified saponin retains the ability to stimulate an immune response in an animal.

36. The substantially pure modified saponin of claim 35, wherein said blocking group is ethylamine.

37. The substantially pure modified saponin of claim 35, wherein said linking group is bifunctional.

38. The substantially pure modified saponin of claim 35, wherein said linking group is selected from the group consisting of: ##STR5## wherein R" is hydrogen, C.sub.1-4 alkyl, or C.sub.1-4 alkyl substituted by phenyl, hydroxyphenyl, indolyl, mercapto, C.sub.1-4 alkylthio, hydroxy, carboxy, amino, guanidino, imidazolyl or carbamyl; or wherein R and R" together form a pyrrolidinyl or piperidinyl ring.

39. The substantially pure modified saponin of claim 38, wherein said linking group is ethylene diamine.

40. The substantially pure modified saponin of claim 38, wherein said linking group is glycine.

41. Substantially pure modified saponin QA-7 which is reduced to an alcohol group at the triterpine aldehyde.

42. The substantially pure modified saponin of any of claims 35-40 in which the saponin is QA-7.

43. The substantially pure modified saponin of any of claims 35-40 in which the saponin is QA-17.

44. The substantially pure modified saponin of any of claims 35--40 in which the saponin is QA-18.

45. The substantially pure modified saponin of any of claims 35-40 in which the saponin is QA-21.

46. The substantially pure modified saponin of any of claims 35-40 in which the saponin is QA-21-V1.

47. The substantially pure modified saponin of any of claims 35-40 in which the saponin is QA-2 1-V2.

48. A method of enhancing an immune response to an antigen in an individual comprising administering the substantially pure modified saponin adjuvant of any one of claims 35-41 by any suitable means, or administering parenterally, intravenously, intramuscularly or subcutaneously an antigen and at least one substantially pure modified saponin selected from the group consisting QA-18, QA-21, QA-21-V1 and QA-21-V2 which is reduced to an alcohol group at the triterpine aldehyde, to said individual in an amount sufficient to enhance the immune response of said individual to said antigen.

49. A pharmaceutical composition useful of inducing the production of antibodies to an antigen in an individual comprising an immunogenically effective amount of an antigen and at least one substantially pure modified saponin of any one of claims 35-41 administered by any suitable means, or an antigen and at least one substantially pure modified saponin selected from the group consisting QA-18, QA-21, QA-21-V1 and QA-21-V2 which is reduced to an alcohol group at the triterpine aldehyde which is administered parenterally, intravenously, intramuscularly or subcutaneously wherein said substantially pure modified saponin is present in an amount sufficient to enhance the immune response of said individual to said antigen.

Brief Summary Text (4):
As a consequence, most physicians rely on the early morning couph sputum specimen as the means of obtaining a lung fluid specimen. This technique is simple and very common. Unfortunately, the cough sputum specimen can be readily contaminated by the normal flora in the mouth, nose, posterior pharynx, and stomach. Furthermore, sputums from patients with pneumonia are very viscous and heterogeneous in nature and therefore difficult to disperse in a reproducible manner. Quantitative analysis of sputum cannot be accomplished on the very viscous heterogeneous sputums because it is generally necessary in quantitative analysis of specimens like sputum to dilute the specimen and thereafter plate minor portions of the specimen on various growth media and then determine the type and number of colonies of microbial organisms which result on the media. Generally, the maximum number of colonies which can be effectively counted on a petri dish is about 300. Furthermore, it has been accepted that normal sputum samples can contain contaminating microorganisms in quantites up to 10.sup.5 per milliliter, whereas, as causative organisms of pneumonia microorganisms are generally present in quantities greater than about 10.sup.6 per milliliter. Therefore, before a sputum specimen can be quantitatively analyzed, it must be diluted in a manner such that the microbial pathogens are uniformly dispersed in the resulting diluted sample. Accordingly, if a minor portion of this diluted sputum specimen is quantitatively analyzed for the type and number of microbial pathogens, the accurate number of microbial pathogens per milliliter of the sputum sample can be accurately calculated.

Brief Summary Text (5):
Thus, in order to reduce the problem of external contamination and heterogeneity of the sputum sample and provide a quantitative sputum analysis, several attempts have been made to digest the sputum specimen with enzymatic and chemical digestants. Several such digestants have been theretofore tried and all of the digestants have one or more of the following disadvantages: expensive; short shelf life; temperature sensitive; toxic to some or many pathogenic organisms; and require long digestion time. For example, a number of proteolytic enzymes have been tested in both purulent and mucoid sputum. Of such enzymatic materials, trypsin, elastase, and chymotrypsin appear the most effective, and enzymes such as bromelain, ficin or papain were only effective at extreme high concentrations, while plasmin has no detectable effect on sputum viscosity. All such proteolytic enzymes appear to be more effective with mucoid sputums than with purulent sputums. The most widely used digestants for quantitative sputum analysis are aqueous solutions of N-acetylcysteine and Cleland's reagent (1,4-dithio-mesoerithritol). In general, Cleland's reagent exhibits greater mucolytic activity than N-acetylcysteine at lower concentrations, but Cleland's reagent generally loses its mucolytic activity in relatively short periods of time in aqueous solution. Furthermore, both of these reagents are somewhat toxic to microbial pathogens at concentrations needed for rapid digestion of sputum.

Brief Summary Text (6):
Consequently most sputum specimens are processed by a nonquantitative streaking technique, which generally involves streaking the heterogeneous sputum specimen on various growth media. These techniques lead to a substantial number of false positive cultures, and in many instances, overgrowth of the pathogenic organisms by contaminating microorganisms.

Brief Summary Text (8):
According to the invention, I have discovered that certain purified saponins exhibit mucolytic activity and will effectively degrade sputum samples including both purulent and mucoid sputums and uniformly disperse microbial pathogens therewithin without harming the pathogens.

Brief Summary Text (9):
According to one embodiment of the subject invention, a novel technique for the

quantitative analysis of sputums is provided which includes the steps of contacting the sputum specimen after it is collected with an effective mucolytic portion of a nontoxic saponin to convert the sputum specimen to a substantially uniform viscosity and mixing the specimen such that any pathogens are uniformly distributed therewithin and thereafter conducting quantitative analysis techniques on the resulting specimen.

Brief Summary Text (17):
As set forth in said patent, U.S. Pat. No. 3,883,425, a technique is provided for removing microbial toxins from saponin which is extracted from a plant source by removing consitutents from an aqueous solution of said saponin which have an apparent molecular weight of less than about 600, e.g., a molecular size in aqueous solution between about 140 to about 600. One technique disclosed in said patent is to form an aqueous solution of a commercial saponin extract from plants and thereafter pass the solution through a microporous filter membrane which has a mean actual pore size no smaller than about 11 angstroms in diameter and no larger than about 24 angstroms in diameter. The aqueous solution which passes through the microporous filter membrane will contain the antimicrobial toxin, and the filter will exclude the saponin material.

Brief Summary Text (18):
I have now found that such purified saponin plant extracts are effective mucolytic agents in that they will efficiently degrade all types of sputum and disperse microbial pathogens therewithin without harming the pathogens.

Brief Summary Text (20):
In addition, it is preferable to add to the resultant mixture of saponin and sputum from about 0.1% by weight to about 20% by weight and more preferably from about 5% by weight to about 10% by weight of an antifoamant which is nondeleterious to microbial pathogens. Suitable such antifoam agents include materials sold under the trademarks of Dow X Antifoam B and Dow X H 10. These agents contain chemical polymers of dimethylsiloxane and a sterilizable, e.g., autoclavable, nonionic emulsifier such as the type sold under the trademark of Triton X. The material sold under the trademark of Dow X H 10 may be preferred since it is very stable to sterilization by autoclaving. The saponin effectively degrades all types of sputum both mucoid and purulent very rapidly to form a mixture of uniform viscosity.

Brief Summary Text (21):
The sputum sample is then thoroughly admixed to uniformly disperse the microorganisms therewithin. If desired, portions of the resulting degraded sputum sample can be plated directly on various media to obtain an improved qualitative sputum analysis which is not subject to the substantial number of false-positive cultures and overgrowth of pathogenic flora by contaminating microorganisms as is the conventional qualitative technique which does not utilize degraded sputum.

Brief Summary Text (22):
When conducting an improved quantitative analysis of sputum in accordance with the subject invention, the saponin treated sputum is diluted as desired, e.g., 1:100-1:1000 with phosphate buffered normal saline, pH 7.2 or any other suitable diluent which will not interfere in the analysis technique and is nontoxic to the microbial pathogens. The resulting diluted specimen is thoroughly admixed to assure uniform distribution of the microbial pathogens throughout the solution. Next, samples of the diluted solution are added to conventional growth media and allowed to incubate. Next, any resulting colonies on the media can be identified and counted and by knowing the extent of dilution of the sputum specimen, the total quantity of different types of microbial pathogens can thereby be easily calculated. Alternately, if desired, the nondiluted specimen can be subjected to microscopic examination.

Detailed Description Text (3):

The other compounds tested for toxicity were Cleland's reagent (1,4-dithio-mesoerithritol), N-acetylcysteine, and sodium lauryl sulfate. These mucolytic agents were prepared in the concentrations and in the growth broth for each of the microorganisms as indicated in Table 1 and tested for toxicity in the same manner as the saponin described above.

Detailed Description Text (10):
As can be seen from Table 1 above, the relatively high concentration of the purified saponin did not kill or inhibit the growth of any of the micoorganisms tested. However, each of the other mucolytic agents tested prevented growth of several of the microorganisms at much lower concentration than the saponin. It should also be noted that even at recommended use concentration of presently used mucolytic agents (0.5% N-acetylcysteine and 0.1% Cleland's reagent) toxicity against several organisms was noted.

Detailed Description Text (20):
a. an interpretation of normal flora (normal level and type of microorganisms found in nasopharyngeal passages) for Alpha streptococcus and Neissera and diphtheroids occurring in the 10.sup.6 and 10.sup.7 range.

Detailed Description Text (21):
b. positive infection for all other nonyeast organisms (other than set forth in (a) above) occurring in the 10.sup.6 and greater range.

Detailed Description Text (22):
c. 10.sup.5 was interpreted as 1-5 organisms found randomly on a set of plates as a possible positive.

Detailed Description Text (23):
10.sup.3 and upon which is 1 to 5 organisms found randomly on a set of plates is a possible positive for Candida Albicans, and a positive for all other yeasts.

Detailed Description Text (25):
As can be seen in Table 2, the routine clinical method and the quantitative method (which utilized the saponin digestion step) were carried out on 80 sputum specimens, and 29 results differed. In 26 cases, the quantitative method found a positive when the routine clinical lab method did not, and in 3 cases, the routine clinical lab method found a positive whose numbers were not high enough to be considered a positive by quantitative standards. It is particularly noted that in 7 patients Haemophilus influenzae was found in the quantitative method on chocolate plates greater than 10.sup.7 per milliliter and was not detected by the routine clinical lab because of overgrowth. This particular organism has great clinical significance in pneumonia. Also, on four occasions, other organisms which constituted double infections were overgrown and not detected by the routine clinical laboratory analysis. Most of the differences in the results set forth in the table were in yeasts shown as positive by the quantitative method, and either not detected or considered light grown by the routine clinical laboratory method.

Detailed Description Text (27):
As can be seen from Table 3, in some cases the throat has the same organisms at the sputum which means that the patient was either colonized or there was perhaps oral contamination in the sputum sample. Repeat cultures and observations on changing counts would possibly enable the physician to differentiate between these two latter possibilities. If colonization is observed, precautions could then be taken to prevent the establishment of a lung infection. Furthermore, in many instances, the quantitative sputum analysis reveals heavy infection wherein the throat analysis of the throat specimen does not. In this latter case, the data would support the conclusion that there is minimal nasopharyngeal contamination and that a lung infection in this case is highly probable.

Detailed Description Paragraph Table (1):

Table 1

Mucolytic Agent and Percent Concentration Type of Saponin Cleland's N-acetylcysteine Sodium lauryl sulfate Organism Growth Broth* 20% 0.1% 0.5% 0.5% 5.0% 2.5% 10.0%

Escherichia coli I 1 ++ +++ -++ +-+ --- +++ +++ Staphylococcus XIII 1 ++ +++ --- ++- --- --- --- Pseudomonas species 1 ++ +++ --- ++- --- +-+ +-+ Candida species 1 ++ +++ -++ +++ --- +-- --- Torulopsis glabrata 1 ++ +++ -+- +++ --- --- --- Streptococcus pyogenes 2 ++ ++ -- +- +- -- -- Streptococcus pneumoniae 3 ++ ++ -- -- -- -- -- Citrobacter freundii 1 ++ +++ +++ -++ --- +++ +++ Klebsiella pneumoniae 1 ++ +++ -++ +++ --- +++ +++ Enterobacter aerogenes 1 ++ +++ -++ +++ --- +++ +++ Salmonella cholerasuis 1 ++ +++ -++ --+ --- +++ +++ Proteus mirabilis 1 ++ +++ -++ +++ --- +++ +++ Listeria monocytogenes 4 ++ +++ ++- +-- --- --- --- Neisseria meningitidis 4 ++ - - - - - - Brucella suis 4 ++ -+ -- +- -- -- -- Bacteroides fragilis 5 ++ ++ +- +- -- -- -- Clostridium perfringins 5 ++ ++ +- +- - - - Propionibacterium shermanii 5 ++ +- +- -- - - -- -- Mycoplasma hominis 6 ++ NT NT NT NT NT NT

*1 grew in rich broth containing 1 wt % glucose. 2 grew in Todd - Hewett broth and thereafter streaked on blood. 3 grew in rich broth containing 1 wt % glucose and thereafter streaked on blood. 4 grew in rich broth containing 1 wt % glucose and thereafter streaked on blood in a CO.sub.2 jar. 5 grew in a peptone yeast glucose maltose broth and thereafter streaked o blood in an anaerobic jar. 6 originally grew in a PPLO broth and thereafter streaked on PPLO agar in a CO.sub.2 jar. NT not tested.

CLAIMS:

1. In a method of detecting the presence of pathogenic organisms in the respiratory tract wherein a sample of lung fluid is obtained and thereafter analyzed for the presence of microbial pathogens, the improvement comprising:

admixing said sample of lung fluid with an effective mucolytic amount to degrade the viscosity of said lung fluid sample and to impart a substantially uniform viscosity to said sample of lung fluid of a nontoxic saponin which has had microbial toxins removed therefrom which exhibit an apparent molecular weight of less than about 600 in an aqueous solution and thereafter thoroughly admixing the resulting sample having said substantially uniform viscosity to uniformly disperse said microbial pathogens therewithin prior to the time that said sample is analyzed.

2. The improved method of claim 1 wherein said nontoxic saponin is admixed with said sample of lung fluid in an amount ranging from about 0.1 to about 20% by weight of said mixtures of lung fluid and saponin.

3. The improved method of claim 1 wherein said nontoxic saponin is admixed with said sample of lung fluid in an amount ranging from about 5 to about 10% by weight of said mixture of lung fluid and saponin.

4. The improved method of claim 2 wherein said nontoxic saponin is contained within an aqueous solution.

5. The improved method of claim 4 wherein said aqueous solution of nontoxic saponin further comprises a minor effective amount of an antifoaming agent which is nontoxic to microbial pathogens.

6. The improved method of claim 5 wherein said sample is analyzed by plating portions of said samples after treatment with said saponin on growth media.

7. In a method of detecting the presence of pathogenic organisms in the respiratory tract wherein a sputum sample is obtained and thereafter analyzed for the presence of microbial pathogens, the improvement comprising:

admixing said sputum sample with an effective mucolytic amount to degrade the viscosity of said sputum sample of a nontoxic saponin which has had microbial toxins removed therefrom which exhibit an apparent molecular weight of less than about 600 in an aqueous solution and allowing the viscosity of said sputum sample to degrade prior to the time that said sample is analyzed.

8. The improved method of claim 7 wherein said nontoxic saponin is admixed with said sputum sample in an amount ranging from about 0.1 to about 20% by weight of said mixture of sputum and saponin.

9. The improved method of claim 1 wherein said nontoxic saponin is admixed with said sputum sample in an amount ranging from about 5 to about 10% by weight of said mixture of sputum and saponin.

10. The improved method of claim 7 wherein said nontoxic saponin is contained within an aqueous solution.

11. The improved method of claim 10 wherein said aqueous solution of nontoxic saponin further comprises a minor effective amount of an antifoaming agent which is nontoxic to microbial pathogens.

12. The improved method of claim 11 wherein said sample is analyzed by plating portions of said samples after treatment with said saponin on growth media.

☐ 7. Document ID: EP 203586 A, AU 8657915 A, CN 8603736 A, DK 8602527 A, ES 8802274 A, JP 62089625 A, PT 82659 A

L18: Entry 7 of 7 File: DWPI Dec 3, 1986

DERWENT-ACC-NO: 1986-320541
DERWENT-WEEK: 198649

TITLE: Pure Lactobacillus fermentum culture - used for treating and preventing gastrointestinal disease in animals

PRIORITY-DATA: 1986US-0863055 (May 14, 1986), 1985US-0738978 (May 29, 1985)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 203586 A	December 3, 1986	E	027	
AU 8657915 A	December 4, 1986		000	
CN 8603736 A	May 20, 1987		000	
DK 8602527 A	November 30, 1986		000	
ES 8802274 A	July 16, 1988		000	
JP 62089625 A	April 24, 1987		000	
PT 82659 A	November 28, 1986		000	

INT-CL (IPC): A61K 35/74; C12N 1/00; C12R 1/22

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw De

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Term	Documents
TETANI	2633
TETANIS	1
TETANUS	12229
CLOSTRID$	0
CLOSTRID	19
CLOSTRIDA	6
CLOSTRIDACEAE	3
CLOSTRIDAE	1
CLOSTRIDAL	22
CLOSTRIDASPPA	2
(L17 AND (TETANI OR TETANUS! OR CLOSTRID$)).PGPB,USPT,USOC,EPAB,JPAB,DWPI.	7

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Previous Page Next Page Go to Doc#

L2: Entry 16 of 128 File: USPT Jul 8, 1997

DOCUMENT-IDENTIFIER: US 5646247 A
TITLE: Merozoite antigens localized at the apical end of the parasite

Application Filing Year (1):
1991

Detailed Description Text (55):
The DAP or DAP-based peptide compounds and constructs or mixtures thereof will be typically formulated in vaccine compositions comprising a pharmaceutically acceptable medium or diluent (e.g. an aqueous solution, preferably at physiological pH). Optionally, the immunogenic ingredient or ingredients can be admixed with or adsorbed to any known pharmaceutically acceptable carrier (e.g. a macromolecule) or adjuvant, such as killed Bordetella, tetanus toxoid, diphtheria toxoid, muramyl dipeptide, aluminum hydroxide, saponin, etc.

L2: Entry 20 of 128 File: USPT Dec 10, 1996

DOCUMENT-IDENTIFIER: US 5583112 A
TITLE: Saponin-antigen conjugates and the use thereof

Application Filing Year (1):
1992

Detailed Description Text (30):
Among the saponin mixtures effective in the present invention are fractions QA-7 and QA-17, QA-7 and QA-18, QA-17 and QA-18, or QA-7, QA-17, and QA-18 administered together. Purified saponins and conjugates thereof may also be administered together with non-saponin adjuvants. Such non-saponin adjuvants useful with the present invention are oil adjuvants (for example, Freund's Complete and Incomplete), liposomes, mineral salts (for example, AlK(SO.sub.4).sub.2, AlNa(SO.sub.4).sub.2, AlNH.sub.4 (SO.sub.4), silica, alum, Al(OH).sub.3, Ca.sub.3 (PO.sub.4).sub.2, kaolin, and carbon), polynucleotides (for example, poly IC and poly AU acids), and certain natural substances (for example, wax D from Mycobacterium tuberculosis, as well as substances found in Corynebacterium parvum, Bordetella pertussis, and members of the genus Brucella), bovine serum albumin, diphtheria toxoid, tetanus toxoid, edestin, keyhole-limpet hemocyanin, Pseudomonal Toxin A, choleragenoid, cholera toxin, pertussis toxin, viral proteins, and eukaryotic proteins such as interferons, interleukins, or tumor necrosis factor. Such proteins may be obtained frown natural or recombinant sources according to methods known to those skilled in the art. When obtained from recombinant sources, the non-saponin adjuvant may comprise a protein fragment comprising at least the immunogenic portion of the molecule. Other known immunogenic macromolecules which may be used in the practice of the invention include, but are not limited to, polysaccharides, tRNA, nomnetabolizable synthetic polymers such as polyvinylamine, polymethacrylic acid polyvinylpyrrolidone, mixed polycondensates (with relatively high molecular weight) of 4'4'-diaminodiphenyl-methane-3,3'-dicarboxylic acid and 4-nitro-2-aminobenzoic acid (See Sela, M., Science 166:1365-1374 (1969)) or glycolipids, lipids or carbohydrates.

L2: Entry 49 of 128 File: USPT Dec 14, 1993

DOCUMENT-IDENTIFIER: US 5270202 A
TITLE: Anti-idiotypic antibodies to human melanoma-associated proteoglycan antigen

Application Filing Year (1):
1991

Detailed Description Text (111):
When used in active immunotherapy, the anti-idiotype antibodies of the present invention are preferably administered in an adjuvant formulation meaning adjuvants, carriers, vehicles and conjugation techniques known or developed by those skilled in the art. Such formulations may incorporate Syntex Adjuvant Formulation-1 (SAF-1), muramyl dipeptide derivatives, lipopolysaccharides, pluronic polymers, Bacillus Calmette-Guerin ("BCG"), liposomes, mineral oil emulsions, alum adjuvants, such as aluminum hydroxide and aluminum phosphate, saponins such as Quil A, immune-stimulating complexes ("ISCOMS"), lipid A, keyhole limpet hemocyanin (KLH), hepatitis core antigen, tetanus toxoid, water-in-oil emulsions, glutaraldehyde crosslinking and other conjugation procedures to conjugate the anti-idiotype antibodies to adjuvants or carriers. Examples of adjuvant formulations incorporating these materials and processes have been described in Steinberger, et al., Experimental Parasitology, 58:223-229 (1984); Morein, Nature 332: 287-288 (1988); Allison, J. Immunol. Methods, 95:157-168 (1986); Clarke, et al., Nature 330:381-384 (1987); Raychaudhuri, et al., J. Immunol. 137:1743 (1986); Eskola, et al., New Eng. J. Med. 317:717-722 (1987); Allison, Bio/Technology 5:1041 (1987); Leonard, et al., Blood 65:1149-1157 (1985); Practical Guide for Use in Affinity Chromatography and Related Techniques (2nd ed. 1983 by Reactiff IBF) pub. Societe Chemique Pointet-Girard, France.

L2: Entry 12 of 128 File: USPT Dec 9, 1997

DOCUMENT-IDENTIFIER: US 5695766 A
TITLE: Highly virulent porcine reproductive and respiratory syndrome viruses which produce lesions in pigs and vaccines that protect pigs against said syndrome

Application Filing Year (1):
1993

Detailed Description Text (50):
The composition containing the present vaccine may be administered in conjunction with an adjuvant. An adjuvant is a substance that increases the immunological response to the present vaccine when combined therewith. The adjuvant may be administered at the same time and at the same site as the vaccine or at a different time, for example, as a booster. Adjuvants also may advantageously be administered to the animal in a manner or at a site or location different from the manner, site or location in which the vaccine is administered. Adjuvants include aluminum hydroxide, aluminum potassium sulfate, heat-labile or heat-stable enterotoxin isolated from Escherichia coli, cholera toxin or the B subunit thereof, diphtheria toxin, tetanus toxin, pertussis toxin, Freund's incomplete adjuvant, Freund's complete adjuvant, and the like. Toxin-based adjuvants, such as diphtheria toxin, tetanus toxin and pertussis toxin, may be inactivated prior to use, for example, by treatment with formaldehyde.